Semaglutide

Section: 18. Medicines for endocrine disorders > 18.5. Medicines for diabetes > 18.5.2. Hypoglycaemic agents

ATC codes: A10BJ06

Indication	Type 2 diabetes mellitus ICD11 code: 5A11
INN	Semaglutide
Medicine type	Biological agent
List type	Core
Additional notes	BMI ≥ 30 kg/m2
Formulations	**Parenteral > General injections > SC:** 0.68 mg per mL ; 1.34 mg per mL ; 2.68 mg per mL
EML status history	First added in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	dulaglutide (ATC codes: A10BJ05) liraglutide (ATC codes: A10BJ02) tirzepatide (ATC codes: A10BX16)
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Biological
Wikipedia	Semaglutide
DrugBank	Semaglutide

Expert Committee recommendation

The Expert Committee recognized that diabetes and obesity currently represent two major global health challenges, with both conditions reaching epidemic proportions in different populations and regions. According to a study by the NCD Risk Factor Collaboration, in 2022, there were an estimated 828 million adults globally living with diabetes. At the same time, the prevalence of obesity has increased globally – more than doubling in adults since 1990 – and now affecting more than 1 billion people. Growth in the prevalence of obesity is most rapid in low- and middle-income countries. Both diabetes and obesity are major contributors to mortality and morbidity, are responsible for substantial disability-adjusted life years and strain health systems worldwide. Notably, the relationship between obesity and diabetes is both causal and cyclical; excess adiposity significantly increases the risk of type 2 diabetes through mechanisms involving insulin resistance and chronic inflammation. Furthermore, diabetes and obesity together exacerbate the risk of cardiovascular diseases, forming a triad of interlinked conditions that influence each other and jointly account for a substantial proportion of preventable deaths. The Committee noted that 30% to 50% of people with type 2 diabetes have established cardiovascular disease and obesity, representing a large global cohort with this triad of comorbidities. The Committee also noted that for people with all three of these conditions, the risk of death is much higher than in people with either diabetes or obesity alone. The Committee noted the evidence from multiple large-scale randomized controlled trials and

systematic reviews that demonstrated the efficacy of GLP-1 receptor agonists and the GLP-1/GIP dual agonist tirzepatide in people with diabetes in improving glycaemic control, reducing the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), reducing the risk of end stage kidney disease, reducing all-cause mortality, improving health-related quality of life and promoting weight loss, compared with placebo. The Committee noted the consistency of benefits across studies. The Committee also acknowledged that, while some degree of benefit was possible in all patients irrespective of risk of cardiovascular diseases, patients with type 2 diabetes with known cardiovascular disease or chronic kidney disease are a high-risk subgroup that is likely to experience the most relevant benefit, with a 10-fold decreased risk of premature death compared with patients at low risk. The large difference in benefit between those at low risk and those at high risk for premature mortality is an important factor that could be used to identify those patients to be prioritized in the introduction of these medicines at the country level. The Committee noted the evidence from the large systematic review demonstrating the efficacy of GLP-1 receptor agonists (particularly subcutaneous semaglutide) and tirzepatide in people with obesity for achieving clinically meaningful weight loss and improving quality of life, compared with lifestyle modification alone. However, the Committee agreed that evidence of benefits in cardiovascular outcomes and mortality in people with obesity without diabetes was currently limited to a single, large, randomized controlled trial of semaglutide versus placebo. While the outcomes of this trial for cardiovascular outcomes were positive, there were more discontinuations due to adverse events in people receiving semaglutide. The Committee noted that the trial reported outcomes after almost 40 months of follow-up and considered that the available evidence on mortality outcomes was still at an early stage and limited. Refer to the summary for the addition of GLP-1 receptor agonists for use in adults with obesity for full details of the Expert Committee’s recommendation for this indication. Overall, the Committee considered that the magnitude of benefits and certainty of evidence for GLP-1 receptor agonists and tirzepatide were greater for people with diabetes than for people with obesity, particularly for important outcomes of cardiovascular events and mortality, upon which the Committee placed greater value than outcomes of glycaemic control and weight loss. Considering the population of people with type 2 diabetes, the Committee identified people with comorbid established cardiovascular disease or chronic kidney disease as being the cohort for whom the net benefit of treatment was the greatest. The Committee then decided to include comorbid obesity (BMI ≥ 30 kg/m2) as an additional eligibility criterion, thereby establishing a defined high-risk cohort of people for whom these medicines should be listed as essential. The Committee’s reasons for identifying a triple target population include: (i) obesity is a condition that can negatively affect both the mental and physical health of people with diabetes, stalling or worsening the health status; (ii) certain molecules within the pharmacological classes of GLP-1 receptor agonists and GLP-1/GIP dual agonists have an important effect on body weight, i.e. substantial weight reductions far exceeding the weight reductions associated with other hypoglycaemic agents on the EML (e.g. sodium-glucose cotransporter 2 inhibitors); and (iii) the need to highlight the importance of obesity as a public health priority one that requires effective treatment and commitment at both scientific and policy levels. The Committee acknowledged that although effective treatments for people with diabetes and established cardiovascular disease are already included on the Model List, these individuals remain at residual risk for future cardiovascular events. The addition of semaglutide and its therapeutic alternatives to existing therapies may offer further risk reduction, while also providing more pronounced weight loss compared with alternatives such as SGLT-2 inhibitors. The Committee noted that semaglutide, liraglutide, dulaglutide and tirzepatide were associated with important cardiovascular benefits in patients with type 2 diabetes. However, the Committee noted that there were important differences between these medicines for weight loss, with semaglutide and tirzepatide being associated with more relevant body weight reductions compared with the others. The Committee noted that the availability and use of semaglutide and tirzepatide are constrained by price that currently limit their use to only well-resourced health-care systems. The Committee acknowledged the current high price of these medicines and noted the reported cost-effectiveness ratios that exceed willingness-to-pay thresholds in many settings, particularly when used in low-risk patients. The Committee also noted the recent or upcoming patent expiry for liraglutide and semaglutide, which will introduce the possibility for biosimilar entry, increased competition and lower prices. The Expert Committee believed that substantial price reductions could be achieved with biosimilar entry and competition, given the size and universality of the market for these medicines. The Committee noted that when a large eligible patient population exists, robust biosimilar competition has consistently proven to be more reliable at sustainably

reducing prices than other price-reduction mechanisms. The Expert Committee therefore recommended the inclusion of semaglutide, dulaglutide, liraglutide and tirzepatide on the core list of the EML as add-on glucose-lowering therapy for adults with type 2 diabetes mellitus and both (i) established cardiovascular disease or chronic kidney disease; and (ii) obesity (BMI ≥ 30kg/m2) which has a significant impact on their physical health and/or quality of life. This recommendation is made based on evidence of a meaningful and favourable balance of benefits to harms in this patient population. Listing is recommended for semaglutide with a square box, with dulaglutide, liraglutide and tirzepatide as specified therapeutic alternatives. The Committee's decision to recommend a square box listing for semaglutide, with dulaglutide, liraglutide and tirzepatide as therapeutic alternatives aims to foster competition among available alternatives. The Committee hoped that having multiple EML-listed options would serve to facilitate the rapid introduction of prequalified biosimilar formulations and would support countries in negotiating lower medicine prices and selecting the product that represent the best value option. The Committee recommended the inclusion of these medicines in the core list to underscore the importance of their availability in the primary care setting. Type 2 diabetes and its complications, including obesity, are managed primarily in primary care. Delaying access by requiring hospital referral can reduce benefits associated with early intervention, adding costs and limiting availability in rural areas or underserved communities. Early and equitable access to these medicines can help reduce residual cardiovascular risk, improve glycaemic control, and support weight management without requiring referral to specialized centres. This approach promotes continuity of care, reduces health system burden, and aligns with WHO's principle of delivering essential interventions as close as possible to where people live. In recognition of the financial implications of including these medicines in national health systems at their current prices, particularly in resource-constrained settings, the Committee emphasized the importance of targeting use in the first instance to those patients in whom the greatest value health benefit can be realized. The Committee also recommended that WHO continue to monitor the evolving landscape of this class of medicines, including benefits associated with use in people with obesity, potential long-term toxicities and approval of oral formulations. The Committee also recommended that WHO work on existing approaches for managing prices and evaluate alternative strategies to improve affordability and access to reduce the global burden of diabetes. The Expert Committee highlighted that its recommendation provides countries with a practical strategy for rolling out GLP-1 receptor agonists in a fair and efficient manner. By prioritizing patients with type 2 diabetes and established cardiovascular or chronic kidney disease—those at highest risk of premature death and major adverse cardiovascular events—the recommendation aligns with principles of maximizing health benefits and reducing harm. This prioritization helps countries allocate limited resources to where the impact will be greatest. At the same time, the Committee recognized that countries with additional resources may consider extending access to other cohorts, such as adults with obesity and elevated cardiovascular risk but without diabetes, where evidence of benefit is emerging. Such a phased approach supports equity, prevents treatment disparities, and ensures that the introduction of these medicines contributes to reducing preventable mortality and morbidity.

Background

In 2017, the Expert Committee considered a review of medicines for second-line therapy for type 2 diabetes, including (but not limited to) GLP1 receptor agonists and sodium–glucose cotransporter-2 (SGLT2) inhibitors, based on an update of the 2013 review by the Canadian Agency for Drugs and Technologies in Health. The Committee did not recommend the inclusion of second-line medicines for type 2 diabetes on the EML and confirmed the role of sulfonylureas as one of the most cost-effective treatments for intensification therapy of type 2 diabetes. However, the Committee noted that SGLT2 inhibitors had shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality. The Committee considered that this finding needed to be confirmed with data from other trials before this class of medicines could be supported for inclusion on the EML (1). In 2021, the Expert Committee reviewed an application presenting new evidence which confirmed the positive effect of SGLT2 inhibitors compared with placebo on: all-cause mortality; cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina); renal outcomes (kidney failure end-stage renal disease and renal death); body weight; and glycated haemoglobin (HbA1c). The Committee noted that the situation was less clear when

comparing SGLT2 inhibitors with GLP-1 receptor agonists, although the SGLT2 inhibitors seemed to be the preferred option as they were consistently associated with favourable results for most cardiovascular outcomes and were administered orally in contrast to GLP-1 receptor agonists that needed to be injected. For SGLT2 inhibitors, the Committee considered that there was high-quality evidence showing clinically beneficial effects in patients with type 2 diabetes who had not achieved appropriate glycaemic control with metformin or a sulfonylurea, particularly in those at high risk of cardiovascular events and/or diabetic nephropathy. Additionally, there was a reasonable safety profile. The Expert Committee therefore recommended the inclusion of SGLT2 inhibitors on the core list of the EML as a second-line therapy. GLP-1 receptor agonists were not recommended for inclusion for second-line therapy for type 2 diabetes at that time (2). In 2023, the Expert Committee considered an application for inclusion of GLP-1 receptor agonists on the EML for the treatment of obesity. The Expert committee did not recommend GLP-1 receptor agonists for weight loss in obesity because of uncertain long-term clinical benefit and safety in this population. The Committee noted the wide use of these medicines in the treatment of type 2 diabetes and advice from the applicant of a planned submission in 2025 for consideration of GLP-1 receptor agonists for use in the treatment of type 2 diabetes (3).

Public health relevance

According to a study by the NCD Risk Factor Collaboration, in 2022, there were an estimated 828 million adults globally living with diabetes.(4). The prevalence is increasing over time and is accompanied by a substantial rise in associated complications, including cardiovascular disease, which remains a leading cause of morbidity and mortality in people with diabetes. Based on previous studies, the weighted prevalence for established or high-risk cardiovascular disease is around 30% in adults with type 2 diabetes (5, 6). In 2021, diabetes was responsible for 1.6 million deaths and 47% of all deaths due to diabetes occurred in people younger than 70 years. Another 530 000 kidney disease deaths were caused by diabetes, and high blood glucose causes around 11% of cardiovascular deaths (7). It is estimated that around 30% of adults with type 2 diabetes have established or are at high risk of cardiovascular disease (5).

Benefits

The application presented brief summaries of randomized trials and systematic reviews of semaglutide and other GLP-1 receptor agonists investigating the effects of the treatments on cardiovascular outcomes and diabetes outcomes. The following summary has been elaborated by the EML Secretariat. Semaglutide The SUSTAIN-6 trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated the cardiovascular outcomes of semaglutide in 3297 participants with type 2 diabetes on a standard-care regimen (8). Participants were randomly assigned to receive weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. At baseline, 83% of participants had established cardiovascular disease, chronic kidney disease or both. The primary outcome was the first occurrence of major adverse cardiovascular events (MACE): a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The primary outcome occurred in 108/1648 (6.6%) and 146/1649 (8.9%) of participants in the semaglutide and placebo groups, respectively (hazard ratio (HR), 0.74, 95% confidence interval (CI) 0.58 to 0.95; $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority). Semaglutide was associated with a significant reduction in the risk of non-fatal stroke (HR 0.61, 95% CI 0.38 to 0.99). No significant differences were seen between treatment groups for non-fatal myocardial infarction (HR 0.74, 95% CI 0.51 to 1.08), cardiovascular death (HR 0.98, 95% CI 0.65 to 1.48) or all-cause mortality (HR 1.05, 95% CI 0.74 to 1.50). Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (HR 1.76, 95% CI 1.11 to 2.78; $P = 0.02$). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment due to adverse events, mainly gastrointestinal. The study concluded that in patients with type 2 diabetes at high cardiovascular risk, semaglutide significantly reduced the rate of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke compared with placebo, confirming the non-inferiority of semaglutide. A manufacturer-sponsored post hoc analysis assessed the consistency of the cardiovascular effect of semaglutide across subgroups at different baseline cardiovascular risk levels in the SUSTAIN 6 trial (9). Subgroup analyses were performed for patients with or without a history of prior myocardial infarction or stroke, and patients with cardiovascular risk factors or

established cardiovascular disease. Point estimates for the HRs were all below 1.0, favouring semaglutide; however, no significant differences were found between treatment groups for each subgroup. The SELECT trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated cardiovascular outcomes of semaglutide in 17 604 participants with obesity and atherosclerotic cardiovascular disease, and a history of heart failure (10). Participants were randomized to receive escalating doses of once-weekly semaglutide over 16 weeks to a target dose of 2.4 mg or placebo. The primary outcomes in the prespecified analysis were time from randomization to first occurrence of: MACE (a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); a composite heart failure outcome (cardiovascular death or hospitalization or urgent hospital visit for heart failure); cardiovascular death; and all-cause death. The study also examined the effects of semaglutide in patients with heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Semaglutide was associated with improvements in all outcome measures in patients with heart failure compared with those without heart failure. The HRs for MACE, the composite heart failure endpoint, cardiovascular death and all-cause death were 0.72 (95% CI0.60 to 0.87), 0.79 (95% CI 0.64 to 0.98), 0.76 (95% CI 0.59 to 0.97) and 0.81 (95% CI 0.66 to 1.00), respectively. In participants with heart failure, semaglutide was also associated with improved outcomes for MACE in both heart failure with preserved ejection fraction (HR 0.69, 95% CI 0.51 to 0.91) and heart failure with reduced ejection fraction (HR 0.65, 95% CI 0.49 to 0.87) groups. Liraglutide The LEADER trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated the cardiovascular outcomes of liraglutide in 9340 participants with type 2 diabetes and high cardiovascular risk (11). Participants were randomized to receive liraglutide (1.8 mg or maximum tolerated dose daily) or placebo, with a median follow-up of 3.8 years. The primary outcome was the first occurrence of MACE (a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The primary outcome occurred in 608/4668 (13.0%) and 694/4672 (14.9%) of participants in the liraglutide and placebo groups, respectively (HR 0.87, 95% CI 0.78 to 0.97; $P < 0.001$ for non-inferiority; $P = 0.01$ for superiority). Liraglutide was associated with a significantly lower risk of death from cardiovascular causes (HR 0.78, 95% CI 0.66 to 0.93) and death from any cause (HR 0.85, 95% CI 0.74 to 0.97). No significant differences were seen between treatment groups for non-fatal myocardial infarction (HR 0.88, 95% CI 0.75 to 1.03) or non-fatal stroke (HR 0.89, 95% CI 0.72 to 1.11). A randomized, parallel-group trial compared the effectiveness of liraglutide, insulin glargine, glimepiride (a sulfonylurea) and sitagliptin (a dipeptidyl peptidase-4 inhibitor) in maintaining target HbA1c levels in 5047 participants with type 2 diabetes receiving metformin (12). The primary outcome was primary metabolic failure of the assigned treatment, defined as HbA1c of 7% or higher at quarterly measurements. Over a mean follow-up of 5 years, 71% of participants experienced primary metabolic failure events, including 860/1262 (68.2%) participants receiving liraglutide, 852/1263 (67.4%) participants receiving insulin glargine, 908/1254 (72.4%) participants receiving glimepiride and 981/1268 (77.4%) participants receiving sitagliptin. In pairwise comparisons, both liraglutide and insulin glargine were associated with a significantly lower risk of primary metabolic failure compared with glimepiride and sitagliptin. No significant difference was seen between liraglutide and insulin glargine. Dulaglutide The REWIND trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated the cardiovascular outcomes of dulaglutide in 9901 participants with type 2 diabetes and either established cardiovascular disease or multiple cardiovascular risk factors (13). Participants were randomized to receive dulaglutide 1.5 mg weekly or placebo, with a median follow-up of 5.4 years. The primary outcome was the first occurrence of MACE (a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). The primary outcome occurred in 594/4949 (12.0%) and 663/4952 (13.4%) of participants in the dulaglutide and placebo groups, respectively (HR 0.88, 95% CI 0.79 to 0.99; $P = 0.02$ for superiority). Dulaglutide was associated with a significant reduction in the risk of non-fatal stroke (HR 0.76, 95% CI 0.61 to 0.95). No significant differences were seen between treatment groups for non-fatal myocardial infarction (HR 0.96, 95% CI 0.79 to 1.16), cardiovascular death (HR 0.91, 95% CI 0.78 to 1.6) or all-cause mortality (HR 0.90, 95% CI 0.80 to 1.01). Systematic reviews A 2023 systematic review and network meta-analysis of 816 randomized controlled trials (471 038 participants) compared the benefits and harms of various pharmacological treatments for adults with type 2 diabetes (14). Primary outcomes included all-cause death, cardiovascular death, non-fatal myocardial infarction, admission to hospital for heart failure and end-stage kidney disease. The analysis found high-certainty evidence that relative to standard treatments, GLP-1 receptor agonists reduced all-cause death (odds ratio (OR) 0.88, 95% CI 0.82 to 0.93) and cardiovascular death (OR 0.87, 95% CI% 0.81 to 0.94). Similar results were also

found for SGLT-2 inhibitors. There was moderate-certainty evidence that GLP-1 receptor agonist reduced the risk of non-fatal myocardial infarction (OR 0.91, 95% CI 0.85 to 0.98), while there was high-certainty evidence for SGLT-2 inhibitors for this outcome (OR 0.90, 95% CI 0.82 to 0.98). There was high-certainty evidence that GLP-1 receptor agonists reduced the risk of non-fatal stroke (OR 0.85, 95% CI 0.77 to 0.94). There was also moderate-certainty evidence that GLP-1 receptor agonists decreased hospital admissions for heart failure (OR 0.91, 95% CI 0.83 to 0.99) and reduced end-stage kidney disease (OR 0.83, 95% CI 0.75 to 0.92) A 2021 systematic review and meta-analysis of eight randomized controlled trials (60 080 participants) evaluated cardiovascular, mortality and renal outcomes associated with GLP-1 receptor agonists in adults with type 2 diabetes (15). The analysis found that GLP-1 receptor agonists significantly reduced MACE (HR 0.86, 95% CI 0.80 to 0.93), all-cause mortality (HR 0.88, 95% CI 0.82 to 0.94), hospital admission for heart failure (HR 0.89, 95% CI 0.82 to 0.98) and a composite kidney outcome (defined as development of macroalbuminuria, doubling of serum creatinine or at least a 40% decline in estimated glomerular filtration rate, kidney replacement therapy, or death due to kidney disease; worsening of kidney function, based on estimated glomerular filtration rate change) (HR 0.79, 95% CI 0.73 to 0.87). A 2020 systematic review and network meta-analysis of 453 randomized trials (320 474 participants) evaluated the comparative effectiveness and safety of 21 glucose-lowering medicines from nine pharmacological classes in adults with type 2 diabetes (16). Most of the studies were industry funded: 134 (41 862 participants) evaluated monotherapy, 296 (264 087) evaluated add-on therapy to metformin and 23 (14 525 participants) evaluated both monotherapy and add-on therapy. Compared with placebo, all treatments were associated with significant reductions in HbA1c. In treatment-naïve patients, subcutaneous semaglutide, liraglutide and dulaglutide were associated with mean differences (MD) of −1.48% (95% CI −2.15% to −0.81%), −1.45% (95% CI −2.18% to −0.72%) and −1.29% (95% CI −1.96% to −0.62%), respectively. Confidence in the estimates was moderate for subcutaneous semaglutide and low for liraglutide and dulaglutide. Among patients receiving metformin-based therapy, MD in HbA1c for subcutaneous semaglutide, liraglutide and dulaglutide were −1.33% (95% CI −1.50% to −1.16%), −0.80% (95% CI −0.89% to −0.70%) and −0.89% (95% CI −1.05% to −0.73%), respectively. Confidence in the estimates was high for the three GLP-1 receptor agonists. For patients at increased cardiovascular risk receiving metformin-based therapy, the meta-analysis found that liraglutide significantly reduced the risk of cardiovascular death compared with placebo (OR 0.78, 95% CI 0.65 to 0.93, moderate confidence in estimate; however, no significant differences were reported for subcutaneous semaglutide or dulaglutide. Additionally, no significant differences were found between subcutaneous semaglutide, liraglutide dulaglutide and placebo for hospitalizations due to heart failure. A 2019 manufacturer-sponsored review presented an overview of the results of the SUSTAIN 1 5 and SUSTAIN 7 efficacy trials of semaglutide versus placebo (SUSTAIN 1, 5 and 6), sitagliptin (SUSTAIN 2), extended-release exenatide (SUSTAIN 3), insulin glargine (SUSTAIN 4) and dulaglutide (SUSTAIN 7) (17). The trials included patients with type 2 diabetes who were inadequately controlled on standard treatments and measured changes from baseline to end of treatment in HbA1c as the primary efficacy endpoint. Across the trials, mean HbA1c decreased significantly from baseline by 1.2–1.5% with semaglutide 0.5 mg and 1.5–1.8% with semaglutide 1.0 mg, compared with < 0.1–0.4% with placebo and 0.5–1.4% with full doses of active comparators. The trials also reported greater reductions in body weight associated with semaglutide compared with placebo and active comparators. Mean body weight reductions were 3.5–4.6 kg with semaglutide 0.5 mg, 4.5–6.5 kg with semaglutide 1.0 mg, 1.0–1.4 kg with placebo, 3.0 kg with dulaglutide and 1.9 kg with sitagliptin and exenatide. A 2018 meta-analysis of the LEADER, SUSTAIN-6 and EXSCEL (exenatide once weekly) trials investigated the overall effect of GLP-1 receptor agonists on MACE and included subgroup analyses in order to identify subpopulations that may show the greatest cardiovascular benefit (18). The meta-analysis found that compared to placebo, GLP-1 receptor agonists were associated with significant risk reductions in MACE (relative risk (RR) 0.88, 95% CI 0.81 to 0.97) and cardiovascular death (RR 0.85, 95% CI 0.75 to 0.95). Reduction in risk of non-fatal myocardial infarction and non-fatal stroke were not significantly different. Subgroup analyses found no significant difference between GLP-1 receptor agonists and placebo for all subgroups with the exception of race, compared with parameters within the same subgroup category. Within the subgroup of race, there were trends towards a reduced risk of MACE in participants of African (RR 0.78, 95% CI 0.60 to 0.99) and Asian (RR 0.35, 95% CI 0.09 to 1.32) origin. A post hoc analysis found that only Asians participants had a significant reduction in risk of MACE from treatment compared with white participants. A 2018 systematic review and meta-analysis of 12 randomized controlled trials

(9501 participants) assessed the efficacy and safety of semaglutide (subcutaneous or oral) versus placebo or active comparators in adults with type 2 diabetes (19). The primary outcome was change from baseline in HbA1c. For subcutaneous semaglutide versus placebo, significant differences were seen in change in HbA1c favouring semaglutide 0.5 mg (weighted mean difference (WMD) −1.01% (95% CI −1.47% to −0.56%) and semaglutide 1 mg (WMD −1.38%, 95% CI −1.70% to −1.05%). Compared with active comparators, significant differences were also seen favouring semaglutide 0.5 mg (WMD −0.63%, 95% CI −0.95% to −0.31%) and semaglutide 1 mg (WMD −0.84%, 95% CI −1.23% to −0.44%). Compared with placebo, significant differences were observed in change in body weight favouring semaglutide 0.5 mg (WMD −2.32 kg, 95% CI −3.19 kg to −1.46 kg) and semaglutide 1 mg (WMD −4.11 kg, 95% CI −4.85 kg to −3.37 kg). Similarly, compared with active comparators, semaglutide was associated with significant differences in change in body weight (WMD −2.28 kg, 95% CI −3.42 kg to −1.14 kg for 0.5 mg semaglutide and WMD −3.78 kg, 95% CI −4.90 kg to −2.66 kg for 1 mg semaglutide). A 2018 manufacturer-sponsored systematic review and network meta-analysis of 26 studies (number of participants not reported) compared the efficacy and safety of once-weekly semaglutide 0.5 mg and 1 mg with other GLP-1 receptor agonists in patients with type 2 diabetes who were inadequately controlled on 1–2 oral antidiabetic medicines (20). Semaglutide 1 mg was associated with significantly greater reductions in HbA1c and weight and greater odds of achieving HbA1c levels of < 7% or ≤ 6.5% compared with all other GLP-1 receptor agonists. Semaglutide 0.5 mg was associated with similar outcomes compared with most comparators. No significant differences were seen between either dose of semaglutide and other GLP-1 receptor agonists for discontinuations due to adverse effects.

Harms

Gastrointestinal side-effects are among the most reported adverse events associated with GLP 1 receptor agonists. These include nausea, vomiting, diarrhoea and constipation (12, 14, 19, 21). In the SUSTAIN trials, the incidence of nausea was significantly higher in the semaglutide groups compared with placebo (8, 17). Pancreatitis is a serious but relatively rare adverse event associated with GLP-1 receptor agonists (19). Clinical trials and post-marketing surveillance have reported cases of acute pancreatitis in patients treated with these agents. Participants with a history of pancreatitis were largely excluded from the main clinical trials. The use of GLP-1 receptor agonists has been associated with an increased risk of diabetic retinopathy (19). A 2021 meta-analysis and meta-regression examined the associations between retinopathy, HbA1c, systolic blood pressure and weight in six GLP-1 receptor agonist cardiovascular outcome trials (22). The meta-analysis showed no association between GLP-1 receptor agonist treatment and retinopathy (OR 1.10, 95% CI 0.93 to 1.30). Univariate meta-regression showed an association between retinopathy and average HbA1c reduction during the overall follow-up. A 0.1% increase in HbA1c reduction was associated with increased log OR for retinopathy at 3 months, 1 year and overall. The study concluded that HbA1c reduction was significantly associated with increased retinopathy risk in the meta-regression of cardiovascular outcome trials of GLP-1 receptor agonists. The magnitude of HbA1c reduction was correlated with retinopathy risk, but the long-term effect of improved glycaemic control on retinopathy was not measured. The SUSTAIN-6 trial reported a higher incidence of diabetic retinopathy complications in the semaglutide group compared with the placebo group (HR 1.76, 95% CI 1.11 to 2.78) (8). Increased risk of diabetic retinopathy has also been reported in other studies (16). The risk of hypoglycaemia with GLP-1 receptor agonists is generally low when these agents are used as monotherapy or in combination with non-insulin antidiabetic medicines (23). Risk increases when GLP-1 receptor agonists are used in combination with insulin or sulfonylureas.

Additional evidence

Evidence for tirzepatide The SURPASS-1 trial was a 40-week, double-blind, randomized phase III trial that evaluated the efficacy, safety and tolerability of tirzepatide monotherapy versus placebo in adults with type 2 diabetes inadequately controlled by diet and exercise (24). A total of 478 participants were randomized 1:1:1:1 to receive tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. The primary efficacy endpoint was mean change in glycated haemoglobin (HbA1c) from baseline to 40 weeks. Each tirzepatide dose was superior to placebo for the primary endpoint, as well as for fasting serum glucose, bodyweight and HbA1c targets of less than 7.0% and 5.9%. For the three doses of tirzepatide, the least-squares mean changes from baseline in HbA1c were

−1.87%, −1.89% and −2.07%, respectively. Mean changes in bodyweight from baseline to 40 weeks were −7.0 kg, −7.8 kg and −9.5 kg for tirzepatide 5 mg, 10 mg and 15 mg, respectively. The most frequently reported treatment-emergent adverse events with tirzepatide were gastrointestinal adverse events. Discontinuations due to gastrointestinal adverse events occurred more frequently in participants receiving tirzepatide. The proportion of participants experiencing serious adverse events was similar between treatment groups. The SURPASS-2 trial was a 40-week, open-label, randomized phase III trial that compared efficacy and safety of tirzepatide with semaglutide in adults with type 2 diabetes (25). A total of 1879 participants were randomized 1:1:1:1: to receive tirzepatide 5 mg, 10 mg or 15 mg once weekly or semaglutide 1 mg once weekly. The primary endpoint was change from baseline to week 40 in glycated HbA1c. Secondary endpoints included change from baseline to week 40 in body weight and in the glycated haemoglobin level from baseline to week 40. Secondary endpoints were change in body weight from baseline to week 40 and HbA1c targets of less than 7.0% and 5.9%. For the primary endpoint, all doses of tirzepatide were superior to semaglutide with estimated treatment differences of −0.15 percentage points (95% CI −0.28 to −0.03) with 5 mg; −0.39 percentage points (95% CI −0.51 to −0.26) with 10 mg; and −0.45 percentage points (95% CI −0.57 to −0.32) with 15 mg. Similarly, for the outcome of change in bodyweight, all doses of tirzepatide were superior to semaglutide. Weight reduction with tirzepatide was dose-dependent with increasing doses associated with greater reductions. The proportions of participants who achieved HbA1c targets were greater in participants receiving tirzepatide. A 2022 meta-analysis of seven randomized controlled trials (7215 participants) of at least 26 weeks duration from the SURPASS clinical development programme for tirzepatide for type 2 diabetes evaluated risk of cardiovascular event with tirzepatide (n = 4887) compared with a pooled comparator group comprising placebo (n = 286), insulin degludec (n = 360), insulin glargine (n = 1000), semaglutide (n = 469) and dulaglutide (n = 213) (26). The primary objective was to compare the time to first occurrence of confirmed four-component major adverse cardiovascular events (MACE-4, i.e. cardiovascular death, myocardial infarction, stroke or hospitalized unstable angina) between tirzepatide and pooled comparator groups. Tirzepatide was associated with numerically lower but statistically non-significant risks of MACE-4 (HR 0.80, 95% CI 0.57 to 1.11), cardiovascular death (HR 0.90, 95% CI 0.50 to 1.61), myocardial infarction (HR0.76, 95% CI 0.45 to 1.28), stroke (HR 0.81, 95% CI 0.39 to 1.68) and hospitalization for unstable angina (HR 0.43, 95%–CI 0.15 to 1.41). A 2024 retrospective cohort study evaluated the effects of tirzepatide compared with GLP-1 receptor agonists on all-cause mortality and secondary outcomes including MACE, a composite of MACE and all-cause mortality, kidney events, acute kidney injury, and major adverse kidney events in 104 308 adults with type 2 diabetes in the United States of America (27). About 10% of participants received tirzepatide. Tirzepatide was associated with significantly lower risk of all outcomes investigated compared with GLP-1 receptor agonist: all-cause mortality (adjusted HR 0.58, 95% CI 0.45 to 0.75); MACE (adjusted HR 0.80, 95% CI 0.71 to 0.91); composite of MACE and all-cause mortality (adjusted HR 0.76, 95% CI 0.68 to 0.84); kidney events (adjusted HR 0.52, 95% CI 0.37 to 0.73); acute kidney injury (adjusted HR 0.78, 95% CI 0.70 to 0.88); and major adverse kidney events (adjusted HR 0.54, 95% CI 0.44 to 0.67). The SUMMIT trial was a 52-week, double-blind, randomized phase III trial that evaluated the effects of tirzepatide on cardiovascular outcomes in 731 adults with heart failure with preserved ejection fraction and obesity (28). Participants were randomized 1:1 to receive tirzepatide up to 15 mg weekly or placebo. Almost half of the participants in each treatment group had type 2 diabetes. Primary endpoints were a composite of death from cardiovascular causes of a worsening heart failure event and change in Kansas City Cardiomyopathy Questionnaire clinical summary score from baseline to 52 weeks. Treatment with tirzepatide was associated with a reduced risk of cardiovascular death or worsening heart failure compared with placebo (9.9% versus 15.3%; HR 0.62, 95% CI 0.41 to 0.95). After 52 weeks, mean change (standard deviation) in clinical summary score was greater in the tirzepatide group (19.5 (1.2)) than the placebo group (12.7 (1.3)); between-group difference was 6.9 (95% CI 3.3 to 10.6).

Cost / cost effectiveness

The application reported lowest available costs per day of treatment from a 2023 analysis of public databases for the proposed medicines in selected countries (refer to Table 12, TRS 1064). A 2024 report by the Médecins Sans Frontières Access Campaign compared the range of lowest monthly prices of diabetes medicines, including GLP-1 receptor agonists, in 12 countries with their estimated cost-based prices. The analysis estimated that injectable

semaglutide could be sold with a profit for US$ 0.89/month, compared to the current global prices being charged of 95–353 United States dollars (US$) per month (30). Biosimilar manufacturing could introduce market competition and lead to substantial price reductions. A 2021 study estimated price targets for incremental costs of switching to newer treatments to achieve cost–effectiveness in low- and middle-income countries (31). The analysis included use of these agents as add-on therapies in a so-called glycaemia-agnostic setting for people with cardiovascular disease, heart failure or chronic kidney disease. The study determined that the cost–effectiveness ratios for SGLT2 inhibitors and GLP-1 receptor agonists could be substantially reduced (by 92% for SGLT2 inhibitors and by 72% for GLP-1 receptor agonists) by targeting treatment to patients with type 2 diabetes with these comorbidities. A 2022 cost–effectiveness study evaluated the lifetime cost–effectiveness of first-line treatment with SGLT2 inhibitors or GLP-1 inhibitors from the United States health-care sector perspective (32). In the base-case analysis, SGLT2 inhibitors were associated with higher costs and more quality-adjusted life years (QALY) compared with metformin, with an incremental cost–effectiveness ratio of US$ 478 000 per QALY gained, while GLP-1 receptor agonists had higher costs and reduced QALYs (i.e. were dominated). In a sensitivity analysis when injection disutility was removed, the incremental cost–effectiveness ratio for GLP-1 receptor agonists was US$ 327 000 per QALY gained. Of note, this study was not designed to evaluate the cost–effectiveness specifically in the subgroup of patients with type 2 diabetes and established or at high risk for cardiovascular disease. A 2024 systematic review evaluated nine cost–effectiveness studies of newer pharmacological treatments for type 2 diabetes (33). The studies were non-industry-funded cost-effectiveness analyses from a United States perspective. Three studies estimated the cost–effectiveness of using GLP-1 receptor agonists as second-line therapy versus various comparators. The review found moderate-certainty evidence that addition of daily oral or weekly injectable GLP-1 receptor agonist was probably of intermediate value with the incremental cost–effectiveness ratios ranging from US$ 50 000 to US$ 150 000 per QALY gained compared with continuing metformin alone. Two studies estimated the cost–effectiveness in the third-line setting (added to metformin and sulfonylureas). The incremental cost–effectiveness ratios were US$ 122 000 and > US$ 150 000 per QALY gained for the addition of a GLP-1 receptor agonist compared with adding no additional treatment or neutral protamine Hagedorn insulin, a dipeptidyl peptidase 4 inhibitor or an SGLT2, respectively. The application stated that due to recent and upcoming patent expirations for GLP-1 receptor agonists, there will be opportunities for multisource manufacturing and meaningful price reductions.

WHO guidelines

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus did not consider GLP-1 receptor agonists as the guidelines excluded non-insulin injectable antidiabetic medicines (29). Various national and international guidelines currently include recommendations for the use of GLP-1 receptor agonists in patients with type 2 diabetes, as listed in the application.

Availability

Semaglutide injection has regulatory and marketing approval in many high-income countries, but regulatory approval and market availability in low- and middle-income countries is more limited and variable. Basic patent expiry is reported for March 2026. Biosimilars are not currently available, although are in development in some countries (e.g. India). Liraglutide has regulatory and marketing approval in many countries globally. Some companies are already marketing biosimilar liraglutide in China, India and the United Kingdom (34). No information was presented in the submission on the availability of dulaglutide.

Other considerations

The Expert Committee considered two separate applications involving GLP-1 receptor agonists: one for the treatment of adults with type 2 diabetes and established or at high risk of cardiovascular disease and one for the treatment of adults with obesity. While keeping the recommendations for the diabetes and obesity applications separate, the Expert Committee evaluated the applications together to better contrast possible differences between benefits and harms for the two conditions and understand the implications of coverage for the two

cohorts of patients at global, regional and national levels. The Committee also recalled that previous applications (in 2017, 2021 and 2023) for inclusion of GLP-1 receptor agonists for use in the treatment of diabetes had been evaluated and not recommended.

Refer to TRS 1064 for reference list.

